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AF/1647
PATENT
Attorney Docket No. 205654

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of:

Kovesdi et al.

Application No. 09/832,355

Filed: April 10, 2001

For: VEGF FUSION PROTEINS

Art Unit: 1647

Examiner: L. Spector

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**TRANSMITTAL OF
APPELLANTS' APPEAL BRIEF**

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In accordance with 37 CFR 1.192, appellants hereby submit Appellants' Brief on Appeal in triplicate.

The items checked below are appropriate:

1. Status of Appellants

This application is on behalf of ☐ other than a small entity or ☒ a small entity.

2. Fee for Filing Brief on Appeal

Pursuant to 37 CFR 1.17(c), the fee for filing the Brief on Appeal is for: ☐ other than a small entity or ☐ a small entity.

Brief Fee Due \$160.00

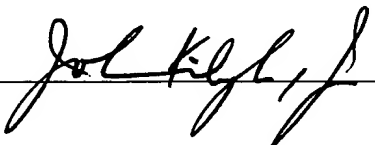
3. Oral Hearing

☐ Appellants request an oral hearing in accordance with 37 CFR 1.194.

CERTIFICATE OF MAILING

I hereby certify that this document (along with any documents referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to: Appeal Brief - Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: September 9, 2003



In re Appln. of Kovesdi et al.
Application No. 09/832,355

4. Extension of Time

- ☐ Appellants petition for a one-month extension of time under 37 CFR 1.136, the fee for which is \$110.00.
- ☒ Appellants believe that no extension of time is required. However, this conditional petition is being made to provide for the possibility that appellants have inadvertently overlooked the need for a petition and fee for extension of time.

Extension fee due with this request: \$

5. Total Fee Due

The total fee due is:

Brief on Appeal Fee	\$160.00
Request for Oral Hearing	\$ 0.00
Extension Fee (if any)	\$ 0.00

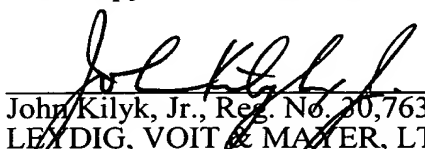
Total Fee Due: \$160.00

6. Fee Payment

- ☐ Attached is a check in the sum of \$.
- ☒ Charge Account No. 12-1216 the sum of \$160.00. A duplicate of this transmittal is attached.

7. Fee Deficiency

- ☒ If any additional fee is required in connection with this communication, charge Account No. 12-1216. A duplicate copy of this transmittal is attached.



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Date: September 9, 2003



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APPELLANTS' APPEAL BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In support of the appeal from the final rejection dated April 25, 2003,
Appellants now submit their Brief.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to GenVec, Inc.

Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal.

Status of Claims

Claims 1-9, 12, 13, 16-28, 30-41, and 43-46 are currently pending. Claims 1-7, 9, 12, 16-19, 30-41, and 43-46 are the subject of this appeal and are set forth in the Appendix attached hereto. Claims 8, 13, and 20-28 have been withdrawn from consideration. Original claims 10, 11, 14, 15, 29, and 42 were canceled in an Amendment filed February 24, 2003.

Status of Amendments

No amendment has been filed subsequent to the final Office Action dated April 25, 2003.

Summary of Invention

The invention defined by the rejected claims is directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain (see paragraphs [0006], [0007], [0023], and [0045]). The first peptide portion can comprise VEGF₁₂₁ (see paragraph [0007]). The second peptide portion can comprise an angiopoietin, a fibroblast growth factor, a member of the HBNF-MK family of growth factors, an alkaline phosphatase, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof (see paragraphs [0050], [0075]-[0077], and [0081]). The invention also is directed to a polynucleotide, that, when expressed, results in the production of the above-described fusion protein (see paragraphs [0109]-[0115]), as well as a vector (e.g., a replication-deficient adenoviral vector) comprising the polynucleotide (see paragraphs [0116] and [0117]).

The invention further provides a method of promoting angiogenesis, bone growth, wound healing, or any combination thereof in an individual. The method comprises administering the above-described fusion protein to the individual in an amount effective to promote angiogenesis, bone growth, wound healing, or any combination thereof (see paragraph [0186]). The invention also is directed to a fusion protein as described above, wherein the VEGF peptide portion is at least about 115 amino acids in length (see paragraph [0081]).

Issues

(a) Whether the invention defined by claim 31 is described in the specification in such a way as to reasonably convey that the inventors had possession of the invention at the time of filing of the present application as required by 35 U.S.C. § 112, first paragraph.

(b) Whether the invention defined by claims 1-7, 9, 12, 16-19, 30-41, and 43-46 is described in the specification in such a way as to (1) reasonably convey that the inventors had possession of the invention at the time of filing of the present application (written description) and (2) enable one of ordinary skill in the art to make and use the invention as claimed (enablement) as required by 35 U.S.C. § 112, first paragraph.

(c) Whether the invention defined by claims 1-4, 9, 16-19, 32-34, 39-40, and 43-45 is anticipated by WO 00/37642 (Davis et al.).

(d) Whether the invention defined by claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 is obvious over Yoon et al., *Life Sciences*, 64(16), 1435-1445 (1997), in view of either or both of U.S. Patent 6,291,667 (Gill et al.) and U.S. Patent 5,874,542 (Rockwell et al.).

Grouping of Claims

The claims do not stand or fall together. The rejected claims can be categorized into eight groups. Group I consists of claims 1-9, 12, 13, 16-19, and 32, which are directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain. Group II consists of claims 20-26, which recite the fusion protein of Group I, further characterized by the second peptide portion comprising a peptide that is about 25% or more homologous to angiopoietin-1. Group III consists of claim 27, which recites the fusion protein of Group I, further characterized by the second peptide portion comprising an acidic fibroblast growth factor or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof. Group IV consists of claims 28, 30, and 31, which recite the fusion protein of Group I, further characterized by the second peptide portion comprising a member of the HBNF-MK family of growth factors or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof. Group V consists of claim 33, which recites a polynucleotide comprising a nucleotide sequence which, when expressed in a cell permissive for expression of the nucleotide sequence, results in the production of the fusion protein of Group I. Group VI consists of claims 34-38, 40, and 41, which are directed to a vector comprising the polynucleotide of Group V and a method of producing a fusion protein using the vector. Group VII consists of claim 39, which recites a method of promoting angiogenesis, bone growth, wound healing, or any combination thereof in an individual comprising administering to the individual the fusion protein of Group I. Group VIII consists of claims 43-46, which recite the fusion protein of Group I, further characterized by the VEGF peptide portion being at least about 115 amino acids in length.

While the pending claims bear some relationship to each other, the claims are nonetheless separately patentable. In this respect, claims 1-9, 12, 13, 16-19, and 32 (Group I) pertain to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion that lacks a collagen binding domain and is covalently associated with the first peptide portion, while claims 20-26 (Group II), 27 (Group III), and 28, 30, and 31 (Group IV) specify that such second peptide portion comprises a portion of angiopoietin-1,

acidic fibroblast growth factor, or a member of the HBNF-MK growth factor family, respectively. The differences between these angiogenic proteins are significant and well known, thereby rendering the claims separately patentable. Claim 33 (Group V) pertains to a polynucleotide that produces the fusion protein of Group I when expressed in a cell, while claims 34-38, 40, and 41 (Group VI) pertain to a vector comprising the polynucleotide. The differences between a fusion protein, a polynucleotide encoding a fusion protein, and a vector comprising a polynucleotide also are significant and well known, thereby rendering the claims of Groups V and VI separately patentable from each other and from the claims of Group I. Claim 39 (Group VII) pertains to a method of promoting angiogenesis, bone growth, wound healing, or any combination thereof in an individual comprising administering to the individual the fusion protein of Group I, while claims 43-46 (Group VIII) pertain to the fusion protein of Group I, further characterized by the VEGF peptide portion being at least about 115 amino acids in length. The fusion protein of Group I does not anticipate or render obvious a method of using the fusion protein, or a fusion protein comprising a VEGF peptide portion 115 amino acids in length, thereby rendering the claims of Groups I, VII, and VIII separately patentable. As such, the claims of the present application do not stand or fall together.

Argument

a. Rejection of claim 31 under 35 U.S.C. § 112, first paragraph (written description)

In the final Office Action dated April 25, 2003, the Examiner maintains that the invention defined by claim 31 is not described in the specification in such a way as to reasonably convey that the inventors had possession of the invention at the time of filing of the present application (written description). In particular, the Examiner contends that there is no support in the specification for the phrase "at least about 60%." Appellants note that paragraph [0063] of the specification discloses that the second peptide portion of the claimed fusion protein comprises about 60% or less of the wild-type HBNF or MK amino acid sequence, as a preferred embodiment. Thus, one of ordinary skill in the art would understand that Appellants had possession of the invention defined by claim 31.

b. Rejection of claims 1-7, 9, 12, 16-19, 30-41, and 43-46 under 35 U.S.C. § 112, first paragraph (written description and enablement)

The Examiner maintains that claims 1 and 43 are not adequately described or enabled by the present specification because promotion of bone growth is not an art-recognized property of VEGF. To support this contention, the Examiner points to specific references

relied upon by Appellants which allegedly do not describe VEGF as a causative factor in the induction of bone growth. Appellants note that the appealed claims do not require that the first non-heparin-binding VEGF-A peptide portion be a *causative factor* in bone growth. Rather, the claims merely require that the first VEGF-A peptide portion *promote* bone growth. The American Heritage College Dictionary, 3rd Edition, Houghton Mifflin Company (2000), defines the term “promote” as meaning “to contribute to the progress or growth of; further” (copy of relevant excerpt submitted herewith). Therefore, Appellants submit, and the prior art supports, that bone growth promotion is a well-known property of VEGF. Indeed, for example, Ferrara et al., *Curr. Opin. Biotech.*, 11, 617-24 (2000) (enclosed herewith), describes the near complete suppression of blood vessel invasion concomitant with impaired trabecular bone formation when VEGF activity is inhibited. Based on these findings, the Ferrara reference concludes that VEGF-dependent blood vessels are *essential* for coupling apoptosis of hypertrophic chondrocytes with bone formation (see, e.g., page 619, left column, first complete paragraph). Accordingly, while the Ferrara reference may not demonstrate VEGF as being a direct *causative factor* in bone formation, VEGF, at the very least, is demonstrated to *promote* trabecular bone formation by stimulating neovascularization necessary for bone growth. Thus, one of ordinary skill in the art would understand that Appellants had possession of the invention defined by claims 1 and 43, and would be able to make and use the invention defined by those claims without undue experimentation using the methods set forth in the present specification.

The Examiner further contends that the specification does not adequately describe or enable the scope of a second non-VEGF peptide portion with angiogenesis or bone growth promoting activity, as required by the pending claims. Appellants point out that Section 112, first paragraph, is satisfied by the disclosure of a representative number of species. A “representative number of species” means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one can describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a “representative number” depends on whether one of ordinary skill in the art would recognize that applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. Description of a representative number of species, however, does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. M.P.E.P. § 2163. *See Cordis Corp. v. Medtronic Ave, Inc.*, 2003 WL 21910747, 11 (Fed. Cir. 2003). Moreover, if a particular claim is enabled by the specification, the applicant need not describe all possible embodiments of that claim. M.P.E.P. § 2164.02. *Chiron Corp. v. Genentech, Inc.*, 2002 WL 32124007, 12 (E.D. Cal.

2002) citing *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

As discussed in the “Response to Office Action” dated February 24, 2003, the present specification discloses tens, if not hundreds, of species within the genus of angiogenesis-promoting and/or bone growth-promoting factors. The disclosed species comprise a broad spectrum of peptides that promote angiogenesis and/or bone growth, including growth factors, cytokines, signaling molecules, and transcription factors, that could be employed as the non-VEGF peptide portion of the claimed fusion protein (see, e.g., paragraphs [0048]-[0056], [0075], and [0081]). Even if there is substantial variation within the genus of factors that promote angiogenesis and/or bone growth, the present specification discloses a sufficient number and variety of species within the genus to reflect the variation therein.

With respect to the alleged lack of enablement, the Examiner contends that, despite the numerous methods for generating the claimed fusion proteins described and exemplified in the present specification, one of ordinary skill in the art could not make and/or use the claimed invention “without knowing what the protein is” (see final Office Action at pages 5 and 6, bridging paragraph). The Examiner appears to imply that, because the claimed invention allegedly is not described by the present specification, it also is not enabled by the present specification. Appellants note the enablement requirement of Section 112, first paragraph, is separate and distinct from the written description requirement (M.P.E.P. § 2164). In this regard, a recited claim element in and of itself may enable one of ordinary skill in the art to make and use the invention defined by the claim, even though the claim element may not be described in the original disclosure (M.P.E.P. § 2164). Thus, a claim must be analyzed for both enablement and written description using their separate and distinct criteria (M.P.E.P. § 2164).

The present specification discloses methods for linking the first and second peptide portions (see, e.g., paragraphs [0086]-[0092]), recombinant DNA methods for producing the fusion protein (see, e.g., paragraphs [00109]-[00117]), and viral gene transfer vectors that encode and express the fusion protein in a suitable host (see, e.g., paragraphs [00116]-[00127]). Appellants also note that methods for generating fusion proteins have been extensively described in the prior art, and such methods are referred to in the present specification. Moreover, the Examples describe methods for generating specific fusion proteins embraced by the claims. The disclosure of angiogenic and bone growth promoting factors in the specification and in the literature, coupled with the disclosed methods for making and using the claimed fusion protein, clearly equips the skilled artisan with the ability to practice the claimed invention using only routine methods of experimentation.

The subject matter of claims 6 and 7 allegedly is not adequately described or enabled by the present specification. The Examiner alleges that the enablement rejection with respect to claims 6 and 7 is predicated in part by the breadth of the claims and the unpredictability in determining protein half-lives.

Contrary to the assertion of the Examiner, the determination of protein half-lives is not unpredictable. In this respect, methods for determining protein half-life have long been known to those skilled in the art, and include, for example, pulse-chase experiments as described in Dandri et al., *J. Virol.*, 72, 9359-64 (1998) (enclosed herewith), and Distelhorst et al., *J. Biol. Chem.*, 264, 13080-85 (1989) (enclosed herewith). Moreover, the specification discloses specific structural features of the claimed fusion protein, the absence or presence of which enhances protein stability. For example, the specification discloses that removal of the Ang-1 coiled-coil domain imparts an increased half-life to a fusion protein comprising Ang-1 as the non-VEGF peptide portion (see, e.g., paragraph [0108], lines 10-14). The specification also indicates that the inclusion of cysteine residues in either or both of the VEGF and non-VEGF peptide portions of the claimed fusion protein renders the fusion protein more resistant to extracellular degradation (see, e.g., paragraph [0108], lines 14-18), thereby enhancing protein stability. Fusion protein half-life also can be extended when the non-VEGF peptide portion comprises an IgG domain, as described in the specification at paragraph [0108], lines 18-22. The specification further discloses a range of half-lives for the fusion protein (including a half-life of at least about 10 minutes as set forth in claim 7), and specifically indicates that the claimed fusion protein exhibits a half-life at least twice as long as the half-life of an Ang-1 protein (see paragraph [00108]). Thus, Appellants submit that the subject matter of claims 6 and 7 is adequately described in the specification such that one of ordinary skill in the art would be able to make and use the present invention using only routine methods of experimentation.

The Examiner alleges that the subject matter of claim 12 is not adequately described or enabled, both generically and with respect to the elected species, HBNF. In particular, the Examiner contends that the specification does not provide guidance as to what types of proteins provide the properties recited in claim 12, and that none of these properties have been recognized in the art as being associated with HBNF. Appellants respectfully disagree with this assertion, and note that claim 12 requires that the second peptide portion exhibit any *one or combination of* the functional characteristics set forth therein. As discussed in the "Response to Office Action" dated February 24, 2003, literature articles published before or shortly after the filing of the present application demonstrate that HBNF (also known as pleiotrophin (PTN) and heparin affinity regulatory peptide (HARP)) induces endothelial cell proliferation, migration, survival, and capillary-like structure formation toward a variety of

endothelial cells (see, e.g., Souttou et al., *J. Cell Physiol.*, 187, 59-64 (2001) (enclosed herewith), and Papadimitriou et al., *Biochem. Biophys. Res. Comm.*, 282, 306-313 (2001) (reference of record)). The Examiner asserts that the Papadimitriou reference cannot be relied upon to establish the state of the art at the time of the invention. Appellants note, however, that both the Papadimitriou and Souttou references were relied upon merely to demonstrate that the angiogenic properties described above are inherent to the HBNF polypeptide. Thus, Appellants maintain that the disclosure of angiogenic promoting factors (e.g., HBNF) in the specification and in the literature, coupled with the disclosed methods for making and using the claimed fusion protein, clearly equips the skilled artisan with the ability to practice the invention defined by claim 12 using only routine methods of experimentation. Accordingly, claim 12 is described and enabled both generically and with respect to the elected species.

The Examiner maintains that the subject matter of claim 17 is not adequately described or enabled, both generically and with respect to the elected species, HBNF. As discussed herein, and in the "Response to Office Action" dated February 24, 2003, the present specification describes numerous proteins that could be employed as the second peptide portion of the claimed fusion protein, and which exhibit one or more of the functional characteristics set forth in claim 17. Indeed, such factors are disclosed in the specification at, for example, paragraph [0048], and include, for example, midkine, TNF- α , iNOS, and angiopoietin. Methods to determine if a potential second peptide portion exhibits any one of the functional characteristics set forth in claim 17 are known in the art and are described extensively in the specification, as are methods for generating the claimed fusion protein. With respect to the elected species HBNF, the Examiner maintains that none of the properties recited in claim 17 has been reported for HBNF. Appellants respectfully disagree with this assertion, and note that claim 17 requires that the second peptide portion exhibit any *one or combination of* the functional characteristics set forth therein. As discussed above, HBNF has been shown to promote angiogenesis by promoting endothelial cell proliferation, migration, survival, and capillary-like structure formation (see, e.g., Souttou et al., *supra*, and Papadimitriou et al., *supra*). These references indicate that endothelial cell migration and the formation of capillary-like tubes require degradation of the extracellular matrix. According to the Examiner, however, these disclosed properties of HBNF do not indicate that that HBNF itself degrades the extracellular matrix. Appellants note that claim 17 merely requires that the second peptide portion *promotes* one or more of the properties recited therein, which Appellants urge is evidenced by the disclosures of the Souttou and Papadimitriou references. Thus, the subject matter of claim 17 encompasses HBNF, and is adequately described and enabled by the present specification.

The Examiner alleges that fusion proteins comprising VEGF and HBNF, such as those encompassed by claims 30 and 31 are not enabled by the specification, in that one of ordinary skill in the art would not expect a soluble protein comprising HBNF to promote bone growth, wound healing, or angiogenesis of normal (i.e., non-tumor) cells. The Examiner further alleges that certain prior art references relied upon by Appellants in the “Response to Office Action” dated February 24, 2003 do not demonstrate the angiogenic, bone growth promoting, or wound healing properties of soluble HBNF. The Papadimitriou reference, however, discloses the angiogenesis-promoting activity of soluble HBNF in a variety of non-tumor endothelial cell types, such as rat adrenal medulla microvascular endothelial cells (RAME), bovine retinal endothelial cells (BREC), and bovine brain capillary endothelial cells (BBC) (see, e.g., page 308, Figure 1, and page 309, Figures 2 and 3). Moreover, Figure 3 of the Imai reference demonstrates that the only cells unresponsive to HBNF were nonosteoblastic (i.e., control) cells. Indeed, the Imai reference concludes that HBNF likely plays a role in bone formation by mediating recruitment and attachment of osteoblasts (see, e.g., page 1113, Abstract, page 1123, right column, and page 1126, left column). With respect to wound healing, Appellants submit that, while the wound healing activity of HBNF may not have been disclosed at the relevant time, such activity is an inherent feature of HBNF, as demonstrated in, for example, Deuel et al., *Arch Biochem. Biophys.*, 397, 162-171 (2002) (enclosed herewith). Accordingly, using the guidance provided by the present specification and the prior art, one of ordinary skill in the art would be able to make and use a fusion protein as set forth in claims 30 and 31.

c. Rejection of claims 1-4, 9, 16-19, 32-34, 39-40, and 43-45 under 35 U.S.C. § 102(a) in view of WO 00/37642 (Davis et al.).

The Examiner maintains that the Davis ‘642 PCT application anticipates the invention defined by claims 1-4, 9, 16-19, 32-34, 39-40, and 43-45 because the Davis ‘642 PCT application allegedly discloses fusion proteins comprising the receptor binding domains of two ligands, including a fusion protein comprising the receptor binding domains of VEGF and angiopoietin (Ang-1), each of which separately promotes angiogenesis.

The Ang-1 peptide portion of the VEGF-Ang-1 fusion protein disclosed in the Davis ‘642 PCT application does not separately promote angiogenesis or bone growth, as required by the aforesaid claims. In this respect, the Davis ‘642 PCT application discloses a fusion protein comprising the receptor binding domains of VEGF and Ang-1 linked by a multimerizing domain, which enables “clustering” of the Ang-1 receptor binding domain. The Davis ‘642 PCT application indicates that Ang-1 “clustering” induces or enhances its biological activity (see, e.g., page 8, lines 9-24). Indeed, the Davis ‘642 PCT application

discloses that monomeric Ang-1 has low affinity for the Tie-2 receptor, as compared to highly clustered (e.g., tetrameric) VEGF-Ang-1 fusion proteins.

Therefore, the non-VEGF peptide portion of the fusion protein disclosed in the '642 PCT application does not separately promote angiogenesis, bone growth, and/or wound healing, as required by claims 1 and 43, but rather requires multimerization to exert its biological activity. Thus, claims 1 and 43, as well as claims 2-4, 9, 16-19, 32-34, 39, 40, and 44-45 dependent thereon, define novel subject matter in view of the Davis '642 PCT application. The foregoing comments are equally applicable to all of the appealed claims, i.e., the claims of Groups I-VIII.

d. Rejection of claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 under 35 U.S.C. § 103(a) over Yoon et al., *Life Sciences*, 64(16), 1435-1445 (1997), in view of either or both of U.S. Patent 6,291,667 (Gill et al.) and U.S. Patent 5,874,542 (Rockwell et al.).

The Examiner maintains that the invention defined by claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 is obvious over the Yoon reference in view of the '667 patent and/or the '542 patent. The Yoon reference purportedly discloses EGF-angiogenin fusion proteins that target tumor cells via EGF receptors, and kill tumor cells via internalization of the angiogenin portion of the fusion protein. The '667 patent allegedly discloses the presence of VEGF receptors on Kaposi's sarcoma cells, and that Kaposi sarcoma cell survival depends on VEGF. The '542 patent allegedly discloses high levels of flk-1 receptor expression in glioblastoma-associated endothelial cells. This rejection is based on the premise that one of ordinary skill in the art would have been motivated by the '667 patent and the '542 patent to substitute VEGF for EGF in the fusion protein disclosed by the Yoon reference for the purpose of killing Kaposi's sarcoma or glioblastoma cells, thereby arriving at the presently claimed fusion protein.

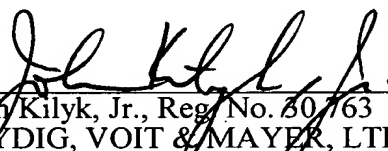
One of ordinary skill in the art, however, would not be motivated to substituted a VEGF of the '667 and '542 patents for EGF in the fusion protein discussed in the Yoon reference. Indeed, the '667 patent and the '542 patent teach away from such a substitution and, thereby, teach away from the present invention. In this respect, the '667 patent discloses methods to induce tumor cell cytotoxicity by inhibiting production of, or signaling by, VEGF. The '542 patent discloses the use of monoclonal antibodies to neutralize VEGF to inhibit angiogenesis. Thus, the '667 patent and the '542 patent teach that VEGF is an agent that promotes tumor angiogenesis. As such, one of ordinary skill in the art seeking to kill tumor cells in accordance with the disclosure of the Yoon reference would not have been motivated by the '667 patent or the '542 patent to substitute a VEGF for EGF in the fusion protein

In re Appln. of Kovesdi et al.
Application No. 09/832,355

disclosed in the Yoon reference, inasmuch as the VEGF peptide portion would enhance tumor cell survival by promoting tumor angiogenesis.

Thus, the subject matter of claims 1-5, 9, 17, 18, 32-34, 41, and 43-46 is unobvious over the Yoon reference, the '667 patent, and the '542 patent, when considered alone or in combination. The foregoing comments are equally applicable to all of the appealed claims, i.e., the claims of Groups I-VIII.

Respectfully submitted,



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Date: September 9, 2003

APPENDIX

1. A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain.

2. The fusion protein of claim 1, wherein the first peptide portion comprises a VEGF-A peptide portion which exhibits a higher affinity for KDR receptors than flt receptors or flk receptors.

3. The fusion protein of claim 2, wherein the VEGF-A peptide portion exhibits about equal or less affinity for neuropilin-1, neuropilin-2, or both, as VEGF₁₂₁.

4. The fusion protein of claim 3, wherein the first peptide portion comprises a wild-type VEGF-A amino acid sequence of about 150 amino acid residues or less.

5. The fusion protein of claim 1, wherein the first peptide portion comprises VEGF₁₂₁.

6. The fusion protein of claim 1, wherein the fusion protein has a half-life in a mammalian host at least twice as long as the half-life of a protein consisting essentially of either the first peptide portion and/or at least twice as long as the half-life of a protein consisting essentially of the second peptide portion.

7. The fusion protein of claim 6, wherein the fusion protein has a half-life of at least about 10 minutes in a mammalian host.

8. The fusion protein of claim 7, wherein the second peptide portion comprises a peptide lacking its native multimerization domain or a peptide comprising a non-functional multimerization domain.

9. The fusion protein of claim 1, wherein the fusion protein is more angiogenic than a protein consisting essentially of the first peptide portion and/or is more angiogenic than a protein consisting essentially of the second peptide portion.

12. The fusion protein of claim 9, wherein blood vessels resulting from administration of the fusion protein to a mammalian host are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration of endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion.

13. The fusion protein of claim 1, wherein the second peptide portion comprises a receptor ligand which is present on a native endothelial cell.

16. The fusion protein of claim 1, wherein administration of the fusion protein to an area in a mammalian host results in greater blood flow in the area of administration than the administration of a protein consisting essentially of the second peptide portion.

17. The fusion protein of claim 1, wherein the second peptide portion comprises a peptide which promotes blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof.

18. The fusion protein of claim 1, wherein the fusion protein is free of any immunoglobulin domains.

19. The fusion protein of claim 1, wherein the second peptide portion comprises an angiopoietin, a fibroblast growth factor, a member of the HBNF-MK family of growth factors, an alkaline phosphatase, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

20. The fusion protein of claim 19, wherein the second peptide portion comprises a peptide that is about 25% or more homologous to angiopoietin-1.

21. The fusion protein of claim 20, wherein the second peptide portion comprises a domain which exhibits about 35% or more homology to the fibrinogen-like domain of Ang-1.

22. The fusion protein of claim 21, wherein the second peptide portion comprises angiopoietin-1 or an angiogenically functional fragment thereof.

23. The fusion protein of claim 22, wherein the second peptide portion comprises an N-terminal truncated form of angiopoietin-1, and the truncated form comprises about 60% or less of the wild-type angiopoietin-1 amino acid sequence.

24. The fusion protein of claim 23, wherein the second peptide portion lacks the multimerization domain of angiopoietin-1.

25. The fusion protein of claim 24, wherein the fusion protein is free of any immunoglobulin domains.

26. The fusion protein of claim 21, wherein the second peptide portion comprises the peptide encoded by KIAA0003.

27. The fusion protein of claim 19, wherein the second peptide portion comprises an acidic fibroblast growth factor or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

28. The fusion protein of claim 19, wherein the second peptide portion comprises a member of the HBNF-MK family of growth factors or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or any combination thereof.

30. The fusion protein of claim 28, wherein the second peptide portion comprises HBNF or MK, or a fragment thereof which promotes angiogenesis, bone growth, wound healing, or a combination thereof.

31. The fusion protein of claim 30, wherein the second peptide portion comprises an N-terminal truncated form of HBNF or MK including at least about 60% of the wild-type HBNF or MK amino acid sequence.

32. The fusion protein of claim 1, wherein:
(a) the amino acid sequence of the first peptide portion or second peptide portion, within about 15 amino acids of the fusion point of the fusion protein, lacks an amino acid residue corresponding to an amino acid residue in its wild-type counterpart, or
(b) the fusion protein further comprises a linker positioned between the first peptide portion and second peptide portion.

33. A polynucleotide comprising a nucleotide sequence which, when expressed in a cell permissive for expression of the nucleotide sequence, results in the production of a fusion protein according to claim 1.

34. A vector comprising the polynucleotide of claim 33.

35. The vector of claim 34, wherein the vector is a replication deficient adenoviral vector.

36. The vector of claim 35, wherein the replication deficient adenoviral vector comprises or expresses a modified adenoviral protein, non-adenoviral protein, or both, which increases the efficiency that the vector infects cells as compared to wild-type adenovirus, allows the vector to infect cells which are not normally infected by wild-type adenovirus, results in a reduced host immune response in a mammalian host as compared to wild-type adenovirus, or any combination thereof.

37. The vector of claim 36, wherein the polynucleotide comprises a nucleotide sequence which upon expression results in a fusion protein comprising VEGF121 fused to (a) angiopoietin-1, (b) an acidic fibroblast growth factor, (c) a HBNF, (d) a MK, (e) an alkaline phosphatase, or (f) a fragment of any of (a)-(e) which promotes angiogenesis, bone growth, or wound healing.

38. The vector of claim 37, wherein the polynucleotide comprises a second nucleotide sequence that, when expressed, produces a second protein which promotes angiogenesis, bone growth, wound healing, or any combination thereof, and wherein the nucleotide sequence which results in the production of the fusion protein is operably linked to a first promoter and the second nucleotide sequence is operably linked to a second promoter, such that the initiation of expression of the first nucleotide sequence and the second nucleotide sequence occurs at different times, in response to different factors, or both.

39. A method of promoting angiogenesis, bone growth, wound healing, or any combination thereof in an individual comprising administering to the individual an amount of the fusion protein of claim 1 effective to promote angiogenesis, bone growth, wound healing, or any combination thereof.

40. A method of producing a fusion protein comprising introducing the vector of claim 34 into a cell such that the nucleotide sequence is expressed to produce a fusion protein.

41. A method of producing a fusion protein comprising introducing the vector of claim 35 into a cell such that the polynucleotide is expressed to produce a fusion protein.

43. A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis, bone growth, wound healing, or any combination thereof, wherein the VEGF peptide portion is at least about 115 amino acids in length and the second peptide portion lacks a collagen binding domain.

44. The fusion protein of claim 43, wherein the second peptide portion promotes angiogenesis.

45. The fusion protein of claim 44, wherein the second peptide portion promotes angiogenesis or bone growth more than wound healing.

46. The fusion protein of claim 45, wherein the fusion protein does not comprise a functional collagen binding domain.